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| EXAMINER | |
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| HILL, KEVIN KAI | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/507,923 | SZPIRER ET AL. | |
| | Examiner | Art Unit | |
| | KEVIN K. HILL | 1633 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *28 October 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *15,16 and 18-42* is/are pending in the application.

4a) Of the above claim(s) *19-21,29-33 and 37-40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15,16,18,22-28,34-36,41 and 42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## Detailed Action

### *Election/Restrictions*

Applicant has elected without traverse the invention of Group I, Claims 15-24 and 26-28, drawn to a recombinant cell or organism having incorporated into genome i) a genetic construct a nucleotide sequence encoding a toxic molecule, and ii) a genetic sequence encoding an antidote molecule to said toxic molecule.

Within Group I, Applicant has elected with traverse the following restricted embodiments:

i) wherein the toxic molecule is ccdB, as recited in claim 18,

ii) wherein the biological organism is a yeast, as recited in claim 22,

iii) wherein the non-toxic compound is an exogenous compound, as recited in claim 24,

iv) wherein the cell compartment comprising a genome within which the genetic construct is integrated is a chloroplast, as recited in claim 27, and

v) wherein the selectable marker is bordered by two different toxic genes, as recited in claim 28.

### *Examiner's Note*

1. **A decision of the petition under 37 C.F.R. 1.144 filed June 10, 2008 has been rendered**, paper entered April 28, 2009, whereupon the petition has been granted-in-part.

The restriction requirement between elected Group I and non-elected Group II is withdrawn.

The restriction requirement between elected Group I/II and non-elected Group III is maintained.

The species election requirement wherein the genetic construct does not or does not comprise a selectable marker, as recited in claim 15(i), is withdrawn.

The species election requirement wherein the genetic sequence encoding the antidote is not added to the construct, as recited in claim 15(ii), is withdrawn.

The species election requirement wherein Applicant has elected the toxic molecule ccdB recited in claim 18, is maintained.

The species election requirement wherein the requirement to elect a biological organism from the groups of organism of plant, animal, mammal, insect or yeast has been reformatted as a requirement to elect a plant, animal or yeast. Applicant elected the yeast recited in claim 22.

The species election requirement wherein the non-toxic compound is an exogenous compound or synthesized by the eukaryotic host cell is maintained. Applicant elected an exogenous compound recited in claim 24.

The species election requirement wherein the cell compartment comprising a genome within which the genetic construct is integrated is maintained. Applicant elected the chloroplast recited in claim 27.

The species election requirement wherein the selectable marker is bordered by two different or identical toxic genes recited in claim 28 is maintained. Applicant elected "two different toxic genes".

The restriction requirement is therefore made FINAL.

## *Amendments*

In the reply filed October 28, 2009, Applicant has cancelled Claims 1-14 and 17, withdrawn Claims 19-21, 29-33 and 36-40, and amended Claims 15, 26, 28, 36 and 42.

Claims 19-21, 29-33 and 37-40 are pending but withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected invention, there being no allowable generic or linking claim.

Claims 15-16, 18, 22-28, 34-36 and 41-42 are under consideration.

## *Priority*

This application is a 371 of PCT/BE03/00045, filed March 19, 2003. Applicant's claim for the benefit of a prior-filed parent provisional application 60/365,938, filed on March 19, 2002 under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged.

The disclosure of the prior-filed application, 60/365,938, filed on March 19, 2002, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. Specifically, 60/365,938 does not support claim 27, wherein the genetic construct is integrated into the genome of a specific cell compartment, specifically a chloroplast. Rather, the provisional application discloses integration into the nuclear genome. The Examiner has found support for the instant claim 27 in the specification [0046] of PCT/BE03/00045, as indicated by Applicant. Accordingly, the effective priority date of claim 27 is granted as March 19, 2003. If Applicant believes 60/365,938 provides support for this disclosure, Applicant should point out such support by page and line number in the reply to this Action.

Claims 15-18, 22-24, 26, 28 and 35 are supported by the disclosure of 60/365,938, filed on March 19, 2002. Accordingly, the effective priority date of claims 15-18, 22-24, 26, 28 and 35 is granted as March 19, 2002.

## *Examiner's Note*

Unless otherwise indicated, previous objections/rejections that have been rendered moot in view of the amendment will not be reiterated. The arguments in the October 28, 2009 response will be addressed to the extent that they apply to current rejection(s).

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

## *Claim Rejections - 35 USC § 112*

2. **The prior rejection of Claim 28 under 35 U.S.C. 112, second paragraph, is withdrawn** in light of Applicant's amendment to the claim.

3. **Claims 15, 18, 22-28, 34-36 and 41-42 are rejected under 35 U.S.C. 112, second paragraph**, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim does not recite the means by which the genetic sequence encoding an antidote molecule (ii) is to be expressed in the host cell. Those of ordinary skill in the art recognize that a desired genetic sequence to be expressed within a desired host cell must be operably linked to a promoter.

Dependent claims are included in the basis of the rejection because although they recite and encompass a genetic sequence encoding an antidote molecule, they do not clarify the means by which the antidote molecule is to be expressed in the host cell.

Appropriate correction is required.

4. **Claim 28 is rejected under 35 U.S.C. 112, second paragraph**, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are: which nucleic acid molecule of Claim 15 is to further comprise a selectable marker? Furthermore, are the two different toxic genes each different than the toxic gene of the first genetic construct?

Appropriate correction and/or clarification is required.

5. **Claim 34 is rejected under 35 U.S.C. 112, second paragraph**, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 34 recites the limitation "further comprises a selectable marker" in reference to "the genetic construct" of Claim 15. There is insufficient antecedent basis for this limitation in the claim because two different genetic constructs *ipsis verbis* (elements (i) and (iii)) in addition to a genetic sequence (element (ii)) which may reasonably be interpreted as a "genetic construct" give that the genetic sequence is a heterologous, recombinant nucleic acid molecule capable of expressing a heterologous polypeptide. Thus, it is unclear which of the at least three nucleic acid molecules recited in Claim 15 is to further comprise a selectable marker.

Appropriate correction is required.

## *Claim Rejections - 35 USC § 102*

6. **The prior rejection of Claims 15-16, 18, 22-26, 28, 34-36 and 41-42 under 35 U.S.C. 102(a) and 35 U.S.C. 102(e)** as being anticipated by Norris et al (U.S. Patent No. 6,271,359) **is withdrawn** in light of Applicant's amendment to Claim 15 to recite "; and (iii) an additional construct…", a limitation that Norris et al do not teach.

## *Claim Rejections - 35 USC § 103*

7. **The prior rejection of Claims 15-16, 22-26, 34-36 and 41 under 35 U.S.C. 103(a)** as being unpatentable over Kristoffersen et al (Appl. Environ. Microbiol. 66(12):5524-5526, 2000) in view of Parekh et al (Biotechnol. Prog. 12:16-21, 1996) **is withdrawn** in light of Applicant's amendment to Claim 15 to recite "; and (iii) an additional construct…", a limitation that neither Kristoffersen et al nor Parekh et al teach.

8. **The prior rejection of Claims 18, 28 and 42 under 35 U.S.C. 103(a)** as being unpatentable over Kristoffersen et al (Appl. Environ. Microbiol. 66(12):5524-5526, 2000) and Parekh et al (Biotechnol. Prog. 12:16-21, 1996), as applied to claims 15-16, 22-26, 34-36 and 41, and in further view of Norris et al (U.S. Patent No. 6,271,359) and Pecota et al (Appl. Environ. Microbiol. 63(5):1917-1924, 1997; *of record in IDS, #89) **is withdrawn** for reasons discussed above.

9. **The prior rejection of Claim 27 under 35 U.S.C. 103(a)** as being unpatentable over Kristoffersen et al (Appl. Environ. Microbiol. 66(12):5524-5526, 2000), Parekh et al (Biotechnol. Prog. 12:16-21, 1996) and Norris et al (U.S. Patent No. 6,271,359) and Pecota et al (Appl. Environ. Microbiol. 63(5):1917-1924, 1997; *of record in IDS, #89), as applied to claims 15-16, 18, 22-26, 34-36 and 41-42, and in further view of Newman et al (Mol. Gen. Genet. 230(1-2):65-74, 1991; Abstract only) and Rochaix (Ann. Rev. Genet. 29: 209-230, 1995) **is withdrawn** for reasons discussed above.

10. **Claims 15-16, 18, 22-26 and 34-36 and 41 are rejected under 35 U.S.C. 103(a)** as being unpatentable over Kristoffersen et al (2000; *of record) in view of Parekh et al (1996; *of record) and Cheo et al (U.S. Patent 7,393,632).

***Determining the scope and contents of the prior art.***

Kristoffersen et al teach a genetically modified yeast having a genetic construct comprising at least one nucleotide sequence comprising a toxic gene, specifically *relE*, under the control of an inducible promoter, specifically GAL1, whereupon expression of *relE* is induced by exogenous, non-toxic compound, galactose, said yeast further comprising a genetic sequence encoding an antidote molecule, specifically *relB*, wherein the art recognizes the prokaryotic *relB* as "not present natively" in yeast, and wherein the genetic sequence encoding the antidote molecule is under the control of an inducible promoter, specifically MET25, whereupon the expression of *relB* is induced by the absence of methionine (pg 5525, col. 1, last ¶), wherein the art recognizes the pYES2 expression vector to be an episomal DNA. The genetic construct comprises a selectable marker, e.g. ura+ or ura+, met+ (pg 5524, Strains), as well as a nucleic acid sequence encoding the antidote (pg 5525, col. 1, last ¶). Kristoffersen et al teach that *relE* strongly inhibits the growth of yeast cells, and thus, absent evidence to the contrary, the yeast host cells necessarily possess a genetic sequence that is or encodes the target of the toxic molecule.

Kristoffersen et al do not teach the genetic construct to be integrated into the genome of the host cell. However, at the time of the invention, Parekh et al taught the use of yeast transformation vectors that integrate into the yeast genome for stable transformation.

The Ty γ integration vectors are recognized in the art to possess long terminal repeats for integration by homologous recombination.

Neither Kristoffersen et al nor Parekh et al teach:

i) an additional construct comprising a nucleic acid to be integrated into the first construct and a nucleic acid sequence which facilitates recombination with a nucleic acid sequence in said first construct, wherein recombination between said first construct and said additional construct prevents toxicity of said first construct; and

ii) the sequence encoding the toxic molecule is flanked by regions allowing homologous recombination.

However, at the time of the invention, Cheo et al disclosed methods for combining three or more nucleic acid molecules for *in vivo* recombination (col. 7, lines 20-25). The host cell may be a yeast cell (col. 22, line 62; col. 25, lines 5-6) and one of the target nucleic acid molecules may exist in the genome of the host cell (col. 22, line 41-col. 23, line 25). The vector may comprise two selectable markers, e.g. the negative selectable marker, ccdB, wherein each selectable marker is flanked by regions allowing homologous recombination (col. 22, lines 54-55; col. 28, lines 1-7). Recombination between the additional genetic construct and the first genetic construct will prevent toxicity of said first construct (col. 74, lines 30-33).

***Ascertaining the differences between the prior art and the claims at issue.***

When analyzed in light of the specification, the nature of the invention is the use of poison/antidote genetic systems, commonly used in prokaryotic host cell systems to facilitate cloning, in eukaryotic host cells, e.g. yeast cells. Prior to the invention, skilled artisans were well aware of integrating and non-integrating yeast transformation vectors. Furthermore, the use of a poison/antidote genetic system had been practiced in yeast cells.

***Resolving the level of ordinary skill in the pertinent art.***

People of the ordinary skill in the art will be highly educated individuals, possessing advanced degrees, including M.D.'s, Ph.D.'s. They will be medical doctors, scientists, or engineers. Thus, these people most likely have both the practical experience in molecular biology and the creation of transgenic cells and organism. Therefore, the level of ordinary skill in this art is high.

"A person of ordinary skill in the art is also a person of ordinary creativity, not an automaton." *KSR International Co. v. Teleflex Inc.*, 550 U.S. ___, ___, 82 USPQ2d 1385, 1397 (2007). "[I]n many cases a person of ordinary skill will be able to fit the teachings of multiple patents together like pieces of a puzzle." Id. Office personnel may also take into account "the inferences and creative steps that a person of ordinary skill in the art would employ." Id. at ___, 82 USPQ2d at 1396.

***Considering objective evidence present in the application indicating obviousness or nonobviousness.***

It would have been obvious to one of ordinary skill in the art to substitute a non-integrating yeast transformation vector as taught by Kristoffersen et al with an integrating yeast transformation vector as taught by Parekh et al with a reasonable expectation of success because the simple substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention. An artisan would be motivated to substitute an episomal transformation vector with an integrating transformation vector because the integrating vector would be stably and predictably propagated into each daughter cell and Parekh et al teach that the integration vector provides more stable expression of a heterologous protein than the episomal vector.

It also would have been obvious to modify the recombinant eukaryotic cell of Kristoffersen et al and/or Parekh et al to comprise an additional construct comprising a nucleic acid molecule to be integrated into the first genetic construct with a reasonable expectation of success because Cheo et al disclosed highly efficient means of achieving the replacement of a toxic gene with a desired nucleic acid molecule of interest using homologous recombination.

The cited prior art meets the criteria set forth in both *Graham* and *KSR*, and the teachings of the cited prior art provide the requisite teachings and motivations with a clear, reasonable expectation of success. Thus, absent evidence to the contrary, the invention as a whole is *prima facie* obvious.

11. **Claim 28 is rejected under 35 U.S.C. 103(a)** as being unpatentable over Kristoffersen et al (2000; *of record) in view of Parekh et al (1996; *of record) and Cheo et al (U.S. Patent 7,393,632), as applied to Claims 15-16, 18, 22-26 and 34-36 and 41, and in further view of Pecota et al (1997; *of record in IDS, #89).

***Determining the scope and contents of the prior art.***

Neither Kristoffersen et al, Parekh et al nor Cheo et al teach the selectable marker to be bordered by two different toxic genes. However, at the time of the invention, Pecota et al taught the construction of a genetic construct comprising a first nucleic acid encoding a toxic protein and a second nucleic acid encoding second toxic protein, wherein the selectable marker is bordered by said first and second nucleic acids encoding toxic proteins (pg 1919, Figure 1, Plasmid maps).

***Ascertaining the differences between the prior art and the claims at issue.***

When analyzed in light of the specification, the nature of the invention is the use of poison/antidote genetic systems, commonly used in prokaryotic host cell systems to facilitate cloning, in eukaryotic host cells, e.g. yeast cells. Prior to the invention, skilled artisans were well aware of poison/antidote genetic systems, as well as their use in eukaryotic yeast cells.

***Resolving the level of ordinary skill in the pertinent art.***

People of the ordinary skill in the art will be highly educated individuals, possessing advanced degrees, including M.D.'s, Ph.D.'s. They will be medical doctors, scientists, or engineers. Thus, these people most likely have the practical experience in molecular biology, the creation of transgenic cells and organism and the use of poison/antidote genetic systems. Therefore, the level of ordinary skill in this art is high.

***Considering objective evidence present in the application indicating obviousness or nonobviousness.***

It would have been obvious to modify the poison/antidote expression system of Kristoffersen et al in view of Cheo et al to comprise a selectable marker bordered by two different toxic genes as taught by Pecota et al with a reasonable expectation of success because Pecota et al teach such a vector design and successfully demonstrated the use of a dual toxic genes in a poison/antidote expression system. It is proper to "take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741,82 USPQ2d 1385, 1396 (2007). See also id. At 1742, 82 USPQ2d 1397 ("A person of ordinary skill is also a person of ordinary creativity, not an automaton."). In

the instant case, the placement of a selectable marker between two toxic genes is an art-recognized design choice. An artisan would have been motivated to modify a poison/antidote expression system to comprise a selectable marker bordered by two different toxic genes because Pecota et al taught at least enhancing plasmid stability for a cloning vector by combining two pairs of independent post-segregational killing loci, in which the two loci are in the same or in opposite transcriptional orientations to each other.

The cited prior art meets the criteria set forth in both *Graham* and *KSR*, and the teachings of the cited prior art provide the requisite teachings and motivations with a clear, reasonable expectation of success. Thus, absent evidence to the contrary, the invention as a whole is *prima facie* obvious.

12. **Claim 42 is rejected under 35 U.S.C. 103(a)** as being unpatentable over Kristoffersen et al (2000; *of record) in view of Parekh et al (1996; *of record) and Cheo et al (U.S. Patent 7,393,632), as applied to Claims 15-16, 18, 22-26, 28 and 34-36 and 41, and in further view of Pecota et al (1997; *of record in IDS, #89).

***Determining the scope and contents of the prior art.***

Neither Kristoffersen et al, Parekh et al, Cheo et al nor Pecota et al teach the first genetic construct comprises LB and RB repeats. However, at the time of the invention, Norris et al disclosed eukaryotic cells, e.g. yeast cells (col. 5, lines 9-12), the instantly elected transgenic cell/organism, comprising a genetic construct comprising at least one nucleotide sequence comprising a toxic gene, wherein said toxic gene is under the control of an inducible promoter, the eukaryotic cell further comprising an anti-toxic genetic sequence encoding an antidote molecule to the poison protein, wherein said antidote molecule is a heterologous ("not natively present") in said eukaryotic cell (col. 8, lines 35-39; col. 30, lines 46-50). The genetic sequence encoding the antidote molecule is under the control of an inducible promoter/operator genetic sequence (col. 6, lines 15-24; col. 8, lines 35-37; col. 29, lines 45-53) that is induced by an exogenous, non-toxic compound, e.g. isopropyl β-D-thiogalactopyranoside (IPTG) (col. 39, Example 6, lines 50-52). Norris et al contemplated a genus of eukaryotic expression vectors (col. 19, lines 1-57), including such genome integrative vectors as baculoviral vectors, tobacco mosaic viral vectors, Ti plasmids, and retroviral vectors (col. 25, lines 21-30), as well as non-integrating vectors (col. 25, lines 43-46). Furthermore, the genetic sequence encoding the antidote is an episomal DNA or non-integrating vectors (col. 25, lines 43-46). Norris et al disclosed the toxic gene CcdB (col. 13, line 34).

Norris et al do not disclose *ipsis verbis* that the sequence encoding the toxic molecule is flanked by regions allowing homologous recombination, wherein the regions allowing homologous recombination are LB and RB repeats. However, those of ordinary skill in the art recognize that the genetic borders of Ti plasmids naturally possess LB and RB repeats (admitted by Applicant; specification, [0015], in reference to Hellens et al and Dennis et al).

***Ascertaining the differences between the prior art and the claims at issue.***

When analyzed in light of the specification, the nature of the invention is the use of poison/antidote genetic systems, commonly used in prokaryotic host cell systems to facilitate cloning, in eukaryotic host cells, e.g. yeast cells. Prior to the invention, skilled artisans were well aware of poison/antidote genetic systems, as well as their use in eukaryotic yeast cells.

***Resolving the level of ordinary skill in the pertinent art.***

People of the ordinary skill in the art will be highly educated individuals, possessing advanced degrees, including M.D.'s, Ph.D.'s. They will be medical doctors, scientists, or engineers. Thus, these people most likely have the practical experience in molecular biology, the creation of transgenic cells and organism and the use of poison/antidote genetic systems. Therefore, the level of ordinary skill in this art is high.

***Considering objective evidence present in the application indicating obviousness or nonobviousness.***

It would have been obvious to one of ordinary skill in the art to substitute a first region allowing homologous recombination as taught by Parekh et al with a second region allowing homologous recombination, e.g. comprising LB and RB repeats, as taught by Norris et al with a reasonable expectation of success because the simple substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention. M.P.E.P. §2144.07 states "The selection of a known material based on its suitability for its intended use supported a *prima facie* obviousness determination in *Sinclair & Carroll Co. v. Interchemical Corp.*, 325 U.S. 327, 65 USPQ 297 (1945)." When substituting equivalents known in the prior art for the same purpose, an express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. *In re Fout*, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). M.P.E.P. §2144.06. In the instant case, those of ordinary skill in the art recognize that regions allowing homologous recombination are functional equivalents for the intended purpose of integrating site-specifically an exogenous nucleic acid into a host genomic nucleic acid molecule. An artisan would be motivated to substitute a first region allowing homologous recombination with a second region allowing homologous recombination because each region allowing homologous recombination is site-specific for different nucleic acid sequences, and depending upon the desired host genetic material to be targeted, the ordinary artisan would use the appropriate homologous recombination regions. A region allowing homologous recombination comprising LB and RB repeats would be applicable to the desired host cell and merely represents a design of choice as per the needs of the artisan.

The cited prior art meets the criteria set forth in both *Graham* and *KSR*, and the teachings of the cited prior art provide the requisite teachings and motivations with a clear, reasonable expectation of success. Thus, absent evidence to the contrary, the invention as a whole is *prima facie* obvious.

13. **Claim 27 is rejected under 35 U.S.C. 103(a)** as being unpatentable over Kristoffersen et al (2000; *of record) in view of Parekh et al (1996; *of record), Cheo et al (U.S. Patent

7,393,632) and Pecota et al (1997; *of record in IDS, #89), as applied to claims 15-16, 18, 22-26, 28, 34-36 and 41-42 above, and in further view of Newman et al (1991; Abstract only; *of record) and Rochaix (1995; *of record).

***Determining the scope and contents of the prior art.***

Neither Kristoffersen et al, Parekh et al, Cheo et al nor Pecota et al teach the genetic construct to be integrated into the chloroplast genome of the host cell. However, at the time of the invention, Newman et al taught the ability to genetically transform the chloroplast genome of the *Chlamydomonas reinhardtii* with an integrating transformation vector, wherein the art recognizes *C. reinhardtii* to be a photosynthetic yeast (Rochaix).

***Ascertaining the differences between the prior art and the claims at issue.***

When analyzed in light of the specification, the nature of the invention is the use of poison/antidote genetic systems, commonly used in prokaryotic host cell systems to facilitate cloning, in eukaryotic host cells, e.g. yeast cells. Prior to the invention, skilled artisans were well aware of poison/antidote genetic systems, as well as chloroplast transformation vectors and protocols in photosynthetic yeasts.

***Resolving the level of ordinary skill in the pertinent art.***

People of the ordinary skill in the art will be highly educated individuals, possessing advanced degrees, including M.D.'s, Ph.D.'s. They will be medical doctors, scientists, or engineers. Thus, these people most likely have the practical experience in molecular biology, the creation of transgenic cells and organism and the use of poison/antidote genetic systems. Therefore, the level of ordinary skill in this art is high.

***Considering objective evidence present in the application indicating obviousness or nonobviousness.***

It would have been obvious to one of ordinary skill in the art to substitute a nuclear integrating transformation vector as taught by Perekh et al and/or Cheo et al with a chloroplast integrating transformation vector as taught by Newman et al with a reasonable expectation of success because the simple substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention. An artisan would be motivated to substitute one integrating transformation vector for another as a matter of optimizing the transformation and stable propagation of a transformation vector in a desired eukaryotic cell type.

The cited prior art meets the criteria set forth in both *Graham* and *KSR*, and the teachings of the cited prior art provide the requisite teachings and motivations with a clear, reasonable expectation of success. Thus, absent evidence to the contrary, the invention as a whole is *prima facie* obvious.

***Response to Arguments***

Applicant does not contest the teachings of Norris et al as applied to the obviousness to substitute a relE/relB poison/antidote genetic system with a CcdB/CcdA poison/antidote genetic

system, nor the teachings of Newman et al and Rochaix et al as applied to the obviousness to substitute a nuclear integrating transformation vector with a chloroplast integrating transformation vector.

## *Double Patenting*

14. **Claims 15-16, 18, 22-24, 26 and 35 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting** as being unpatentable over claims 1-3, 9-10, 13-16 and 22 of copending Application No. 11/558,856 (U.S. 2008/0182327 A1; amendment filed April 6, 2009. A Notice of Allowance was mailed May 22, 2009.)

Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the co-pending application reasonably embrace or are anticipated by the instant claims.

With respect to Claims 15, 16 and 26, the co-pending application claims (claim 1) a recombinant cell comprising a first nucleic acid sequence coding for a poison protein operably linked to a first regulatory sequence and a second nucleic acid sequence encoding an antidote to said poison protein operably linked to a second regulatory sequence, wherein the first nucleic acid sequence is located in the chromosome of the cell. The first regulatory sequence is an inducible promoter, inducible by an exogenous chemical compound (claims 14-16).

With respect to Claims 18, the toxic protein may be ccdB (claim 13), wherein those of ordinary skill in the art recognize that the ccdB toxic protein is derived from the *E. coli* F sex factor plasmid (claims 9-10).

With respect to Claims 22, the host cell is a yeast cell (claim 22).

With respect to Claims 23-24, the inducer is an exogenous chemical compound (claims 14-16), wherein the specification discloses said inducer may be a non-toxic compound, e.g. IPTG [0110].

With respect to Claims 35-36, the nucleic acid sequence encoding the antidote is in an episomal DNA (claim 3) or present in the chromosome (claim 2).

Thus, the recombinant cell comprising the recombinant nucleic acid molecule(s) in '856 are reasonably embraced and/or anticipated by the instantly claimed recombinant cell comprising the recombinant nucleic acid molecule(s).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

## *Conclusion*

15. No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a).

Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Kevin K. Hill whose telephone number is 571-272-8036. The Examiner can normally be reached on Monday through Friday, between 9:00am-6:00pm EST.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Joseph T. Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Kevin K. Hill/
Examiner, Art Unit 1633